REMARKS

Applicants and their undersigned representative respectfully acknowledge the time and courtesy extended by the Examiner, Dr. Ewoldt, in conducting the Interview of November 13, 2001. The discussion at the Interview is essentially reflected in the above amendments and remarks below. Particularly, it was discussed how the claims would be distinguished from the Belkowski disclosure, what data showed unexpected results for the claimed invention and what new method of use claims would be appropriate.

The Amendments

The existing composition and kit claims were amended to recite that they are in "non-injectable" forms. Support for these amendments is found, for example, at page 5, second full paragraph, of the specification which discloses the **optional** use of injectable forms, thus, supporting the use of non-injectable forms. Support for the new claims is found, for example, also at page 4, lines 6-13; page 5, second full paragraph; page 6, first full paragraph; page 7, all three paragraphs; and page 11, first two full paragraphs. It is respectfully submitted that the new method of use claims, which are dependent on the composition and kit claims, should – if restricted – be rejoined with the composition and kit claims upon a finding of allowability of the composition and kit claims.

The amendments do not narrow the scope of the claims and/or were not made for reasons related to patentability. The amendments should not be interpreted as an acquiescence to any objection or rejection made in this application. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The First Rejection under 35 U.S.C. §103

The rejection of claims 12-19 under 35 U.S.C. §103 as being obvious over Belkowski (1991 article) is respectfully traversed.

Belkowski is directed to assessing the effects of Perna canaliculus extract (PCE) on collagen induced arthritis. Belkowski tested the effects in rats having collagen-induced arthritis of: (a) orally administered PCE alone, (b) orally administered PCE together with injected dimethylglycine (DMG) and, (c) a control group. The test results of Table 3.1 show that PCE alone (i.e., Perna) was effective for reducing occurrence and severity (average paw size) of arthritis in the rats. When combined with DMG, however, the combination was less effective than PCE alone in reducing the occurrence of arthritis. Also, the combination had no effect of significance over the control in reducing the severity of arthritis.

At the above-mentioned Interview, the Examiner brought up the issue of whether Belkowski actually anticipates the instant claims. This is certainly not the case, however, since Belkowski does not disclose a composition or kit which contains "non-injectable" forms of both PCE and DMG. Only the DMG is injected in the Belkowski experiments. It is additionally noted that Belkowski does not disclose a mixed composition of PCE and DMG, nor does it disclose a kit of the two components. Also, Belkowski does not disclose or suggest methods using PCE and DMG together to treat lupus (new claims 22-29) or to provide the immune response modification recited in new claims 30-37. These distinctions, at least, preclude Belkowski from being anticipatory of the instant claims. They also preclude Belkowski from rendering the claimed invention obvious under 35 U.S.C. §103 for the reasons which follow.

Belkowski cannot render the instant claims obvious because it does not motivate modification of Belkowski to arrive at applicants' invention. The art – i.e., Belkowski itself –

directs one of ordinary skill in the art away from making such modifications. The data generated by Belkowski clearly teach to one of ordinary skill in the art that, for Belkowski's objective of treating collagen-induced arthritis, the combination of DMG with PCE is detrimental to the effect achieved by PCE alone. Thus, Belkowski is contrary to motivating one of ordinary skill in the art towards combinations of PCE and DMG. While Belkowski still discloses separate oral administration of PCE and injection of DMG for its specific embodiment, there would be no motivation to one of ordinary skill in the art to modify this disadvantageous embodiment of Belkowski to provide combinations of PCE and DMG other than the specific one disclosed. The specific embodiment disclosed by Belkowski does not fall within the literal scope of applicants' claims. Accordingly, Belkowski does not support a rejection of the instant claims under 35 U.S.C. §102 or 35 U.S.C. §103.

As to the new method claims, these are dependent on the composition and kit claims and, thus, distinct for the reasons discussed above. They are further distinct in that Belkowski provides no disclosure regarding methods for treating lupus or modifying the immune response as recited in applicants' method claims.

For the above reasons, it is urged that the art rejection based on Belkowski should be withdrawn.

The Second Rejection under 35 U.S.C. §103

The rejection of claims 12-19 under 35 U.S.C. §103 as being obvious over U.S. Patent No. 5,026,728 (Kendall et al.) in view of Caughey (1983 article) or Gibson (1980 article) or U.S. Patent No. 4,455,298 (McFarlane et al.) is respectfully traversed.

The rejection was made on the basis that the Kendall '728 patent teaches the use of DMG to treat inflammatory conditions, particularly arthritis, that the secondary references each teach the use of PCE-containing compositions to treat inflammatory conditions,

particularly arthritis, and, therefore, it would have been obvious to combine the use of DMG and PCE for treating an inflammatory condition, particularly arthritis.

Even if the basis for rejection is assumed to be correct (although applicants do not admit this), data of record establish significant advantages of the combination of applicants' invention which would not have been expected from the prior art. These unexpected advantages convincingly prove the nonobviousness of the claimed invention.

The specification provides side-by-side data comparing immune responses in a lupus mouse model for a DMG-PCE non-injected combination (oral) according to the invention, for DMG orally alone and for PCE orally alone; see particularly Example 2 and Figures 2-5 of the instant specification. The data as a whole convincingly show that the combination of DMG/PCE provides an advantageous result which is not merely the expected combined effect of DMG and PCE alone but an effect which is **different in kind** than what would have been expected in the prior art.

Figure 2 shows that il-10 cytokine production is **increased** with DMG alone and only slightly decreased, if any (see error limits), with PCE ("PERNA") alone. But the il-10 production is surprisingly **significantly decreased** by the combination of DMG and PCE according to the invention. Figure 2 also shows that TNF-alpha levels are **decreased** with either of DMG or PCE alone but, surprisingly, **increased** by a combination of DMG and PCE. Thus, the data establish that the combined effect of DMG/PCE is not what would have been expected based on the effect shown by DMG or PCE alone.

The significance of this distinct result is discussed in Example 2; see page 11, first two full paragraphs. The effects shown for the combination of DMG/PCE in il-10 and TNF-alpha production are indicative of a shift from a Th2 type response to a Th1 response for these cytokines. Such a shift is of high significance to the immune response generated. See the attached excerpt from Cellular and Molecular Immunology, 3rd. ed, Chapter 12:

Cytokines, pp. 271-272, discussing that Th1 and Th2 are the two dominant subsets of cytokine profiles exhibited in immune responses. Accordingly, the demonstrated shift from a Th2 to Th1 type response for these cytokines effected by the DMG/PCE combination is an unexpected result of high significance to the immune response exhibited.

The advantage of the DMG/PCE combination is further demonstrated in Figures 3, 4 and 5 which in each case show an advantage of the DMG/PCE combination over either of DMG or PCE alone in reducing CD8 and CD19 lymphocytic markers, reducing anti-dsDNA antibody levels, and reducing anti-ssDNA antibody levels. The CD19 results, anti-dsDNA antibody #1 and anti-ssDNA antibody results again show an effect from the combination different from that which would have been expected looking at the results for DMG and PCE separately.

Moreover, these test results represent a comparison against the "closest" prior art, i.e., use of DMG and PCE orally, alone. Under the alleged *In re Kerkhoven* rationale (see Office Action mailed September 26, 2000), the expectation in the art was that the result of the combined use of DMG and PCE should be the same as that for DMG alone and PCE alone in comparable amounts. This is what was compared in the Example 2 tests. Belkowski's teachings are clearly further away from the claimed invention despite that DMG (injected) and PCE (orally) were both administered because Belkowski explicitly establishes that the combination does not work, i.e., it establishes an expectation in the art – from worse results – further away from the invention than that established under the *Kerkhoven* rationale – same results. Additionally, Belkowski differs in the mode of administration of DMG. Clearly then, the closest prior art under *Kerkhoven* are the teachings of using DMG alone, orally, and PCE alone, orally, which is the comparison applicants provided.

The data as a whole in the specification establish that the combination of DMG/PCE provides a significant and unexpected advantageous result over what would have been

expected from the closest prior art teachings of use of either alone, e.g., orally or together as in Belkowski. The combination provides a result, which is different in kind from that expected by combining the effects of DMG and PCE administered alone. The data, thus, proves nonobviousness even if the prior art provided a *prima facie* case for making the combination of DMG/PCE.

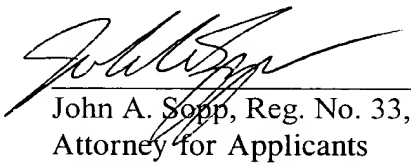
For this reason at least, the rejection under 35 U.S.C. §103 based on the combination of the Kendall '728 reference with Caughey or Gibson or McFarlane '298 should be withdrawn.

Additionally, it is urged that the method of use claims, particularly the method to treat lupus, is further distinguished from the prior art since the art fails to suggest combining DMG and PCE for treating lupus. While Kendall '728 provides a generic teaching which includes lupus in a list of autoimmune diseases treatable using DMG, the secondary references directed to the use of PCE provide no suggestion to use PCE for treating lupus. Thus, while there, arguably, may be a *prima facie* case to combine DMG and PCE to treat arthritis (overcome by the data above), there is no such *prima facie* case for treating lupus. Accordingly, the claims directed to methods for treating lupus are even further distinguished from the prior art.

Similarly, the prior art fails to teach or suggest a method for effecting the immune response recited in new claims 30-37. As discussed above, it has been shown that, in fact, DMG and PCE alone effect immune responses differing from that of the combination recited in these new claims.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

Respectfully submitted,



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VERSION WITH MARKINGS WITH SHOW CHANGES MADE

Claims 12 and 15 have been amended to read as follows:

12. (Twice Amended) A composition comprising a dimethylglycine component and at least one *Perna canaliculus* component, both in a non-injectable form for administration.

15. (Twice Amended) A kit comprising a dimethylglycine formulation in a non-injectable form and a *Perna canaliculus* formulation in a non-injectable form, wherein the *Perna canaliculus* formulation comprises at least one *Perna canaliculus* component.